60. (New) The method of claim 59 which comprises delivering a predetermined quantity of said crystals into a gelatin capsule.

53 61. (New) The method of claim 59 which comprises compressing a pharmaceutically acceptable excipient with said crystals.

## REMARKS

Reconsideration of this application, as amended, is respectfully requested.

## I. Status of the Claims

Claims 1-61 are pending.

Claims 1-35 are amended. New claims 36-61 have been added.

Each of the amended and new claims has written support in the specification and no new matter has been added to the application by this amendment.

Claims 1-35 have been amended to more clearly recite the claimed subject matter and to put the claims in better conformity with U.S. practice. Written support for each of amended claims 1-35 appears in the specification at claims 1-35, as filed.

Written support for each of new claims 36-59 appears in the specification and in the claims, as filed; support for new claims 36 and 37 appears in the specification at page 6, lines 8-12 and at claim 5, as filed; support for new claims 38 and 39 appears in the specification at page 6, lines 19-23 and at claim 6, as filed; support for new claim 40 appears in the specification

at page 7, lines 1-5 and at claims 8 and 9; support for new claims 41-43 appears in the specification at page 7, lines 17-19 and at claim 15, as filed; support for new claims 44-45 appears in the specification at page 7 , lines 17-19 and at claim 19, as filed; support for new claims 46-47 appears in the specification at page 7, lines 17-19 and at claims 20-21, as filed; support for new claims 48-49 appears in the specification at page 7, lines 27-31 and at claim 26, as filed; support for new claims 50-51 appears in the specification at page 8 , lines 2-4 and at claim 27, as filed; support for new claims 52-53 appears in the specification at page 7, line 31 to page 8, line 29; support for new claims 55-56 appears in the specification at page 8 , lines 4-9 and at claim 30, as filed; support for new claims 57-58 appears in the specification at page 8, lines 9-14 and at claim 32, as filed; support for new claim 59 appears in the specification at page 7, line 24, to page 8, line 16 and at page 10, Example 5; support for new claim 60 appears in the specification at page 5, lines 21-23, and support for new claim 61 is found on page 6, lines 8-31.

## II. Rejections under 35 U.S.C. §112(¶2)

Claims 1-33 stand rejected as indefinite, on the grounds that the term "characterized in that" renders the claim indefinite. Applicants submit that the claims have been amended to recite "wherein" instead of "characterized in that." Since the claims no longer recite characterized in that, rejection of the claims on this basis is not proper. Withdrawal of the claim rejections is requested.

Claim 34 stands rejected as indefinite, on the grounds that the word "based" renders the claim indefinite. Applicants submit that the term "based" was a typographical error which has

been corrected in the present amendment. Amended claim 34 now recites "base" instead of "based. Withdrawal of the claim rejection on this basis is requested.

Claim 35 stands rejected as indefinite, on the grounds that the term"dosage from" renders the claim indefinite. Applicants submit that the term "dosage from" was a typographical error which has been corrected in the present amendment. Amended claim 35 recites "dosage form" instead of "dosage from."

In view of the foregoing, Applicants respectfully request that the above referenced indefiniteness rejections be withdrawn.

## III. Rejections under 35 U.S.C. §102(b)

Claims 1-35 stand rejected as anticipated by Boegesoe *et al.* (U.S. Patent 4,943,590) and Boegesoe *et al.* (U.S. Patent 4,136,193). The Examiner takes the position that the cited references disclose the claimed pharmaceutical compositions.

The Examiner is respectfully reminded that according to the Court of Appeals for the Federal Circuit, in *Motorola Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997)), "[f]or a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art." The court stated that although the disclosure requirement of anticipation "presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there." *Id.* at 1490.

Claims 1-15 and 34-35 (and new claims 36-43) are directed to solid unit dosage forms comprising citalopram (or a pharmaceutically acceptable salt) and an excipient by direct compression of citalopram, or by filling a hard gelatin capsule. The cited '590 and '193 references do not teach either of these dosage forms. The references disclose the synthesis and methods of using citalopram and its enantiomers, but nowhere describe citalopram dosage forms which are formed by direct compression or filling citalopram in a hard gelatin capsule. As a result, it is improper for the Examiner to read any suggestion of using citalopram in a dosage form formed by direct compression or citalopram in hard gelatin capsules into the cited references, when these references clearly lack such a teaching.

Claims 16-19 (and new claims 44 and 45) are directed to crystals of citalopram having a median particle size of 40μm. The '590 and '193 patents do not disclose every element of the claimed crystals, since there is no description of citalopram crystals with a median particle size of at least 40μm. It is improper for the Examiner to read into the cited references any hint or suggestion of the use of crystals with a median particle size of at least 40 μm.

Claims 20-33 (and new claims 40-58 and 60) are directed to methods of making citalopram crystals, and call for formation of citalopram crystals with a median particle size of at least 40μm, and require cooling steps and crystallization of citalopram by seeding crystallization with crystals of citalopram. There is no description or suggestion of these method claims in the '590 and '193 patents.

In view of the foregoing, rejection of claims 1-35 as anticipated by the references is improper. Withdrawal of the rejections is respectfully requested.

## IV. Rejections under 35 U.S.C. §103

Claims 1-35 stand rejected as obvious over Bymaster *et al.* (U.S. Patent 6,147,072). The Examiner states that Bymaster teaches using citalopram in a combination therapy for treatment of psychosis (col. 9, l. 18-19) but does not exemplify any pharmaceutical compositions comprising citalopram. The Examiner takes the position that "it would have been obvious to one skilled in the art to prepare instant pharmaceutical compositions (tablets) by direct compression of citalopram based on the teachings of Bymaster."

Applicants respectfully traverse this rejection.

First, the rejection does not amount to *prima facie* obviousness. To establish a *prima facie* case of obviousness, there must be some suggestion or motivation to modify the reference to arrive at the claimed invention. The required teachings or suggestions cannot come from applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). In establishing *prima facie* obviousness, the Examiner must support the assertions of obviousness by specifically indicating where the suggestion to modify the teachings in the reference are found. Applicants submit that the Examiner has not met the requirements for establishing *prima facie* obviousness.

Bymaster does not provide any motivation to prepare the claimed dosage forms. The Examiner neglects to explain how the cited reference provides any motivation to alter the pharmaceutical compositions which are disclosed to arrive at the claimed citalopram tablets (formed by direct compression) or the claimed hard gelatin capsules (comprising citalopram). At no point does Bymaster suggest that such a modification would be beneficial or would yield a useful composition. At best, it would have been obvious to try varying several parameters of the Bymaster

compositions (*e.g.*, active ingredient used and method of tablet formation) until a successful result is attained, since the reference provides no direction whatsoever as to which of many possible choices is likely to be successful. In view of Bymaster, a practitioner would be required to select from possibly dozens of methods of making pharmaceutical compositions, with no guidance whatsoever as to which method to choose, to arrive at the claimed tablet and capsule compositions.

The claims are not obvious because the cited reference fails to provide any motivation to modify the Bymaster compositions to arrive at the claimed compositions or any hint as to how to go about performing such a modification, such that one of skill in the art would have a reasonable expectation of successfully arriving at the claimed invention.

The Court of Appeals for the Federal Circuit stated in *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992) that the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. To satisfy this burden, the Examiner *must* show some objective teaching from the prior art that would lead an individual to combine relevant teachings of the references, and cannot rely on impermissible hindsight to arrive at a determination of obviousness. *See Fritch*, 23 U.S.P.Q.2d at 1784. The mere fact that the teaching of a reference may be modified so as to achieve the claimed invention does not render the claimed invention obvious unless the prior art suggests the desirability of the modification. *Id.* at 1783-4.

Claims 16-19, which are directed to citalopram crystals with a median particle size of at least 40μm, and claims 20-33, which are directed to a method for forming citalopram crystals, are not obvious because Bymaster does not teach nor suggest the claimed crystals, nor a method for

manufacturing the crystals. Furthermore, in the rejection the Examiner makes no reference whatsoever to citalopram crystals or a method for manufacturing the crystals.

Bymaster does not disclose anything about the specific structural form of citalopram, nor does it disclose crystallized citalopram or citalopram crystals with a median particle size of 40μm. There is not even the faintest hint in Bymaster that citalopram crystals with a median particle size of 40μm would be useful or desirable. Furthermore, Bymaster makes no mention of any methods by which citalopram crystals with a median particle size of at least 40μm may be prepared. Thus each of the limitations of the claims are not taught or suggested in the reference. Applicants submit that the Examiner has not established a *prima facie* case that the claims are obvious.

In conclusion, the Examiner has not indicated where Bymaster teaches or suggests modifying the reference to arrive at a compressed citalopram dosage form or citalopram crystals. Clearly the suggestion to provide the claimed dosage form or crystal form of citalopram comes form applicants' disclosure. This is an improper basis for an obviousness rejection. On these grounds, Applicants submit that the a *prima facie* case of obviousness has not been established.

Even if the Examiner concludes that the teachings of Bymaster render the claimed invention *prima facie* obvious, the claimed invention demonstrates unexpected favorable results over the limited teachings of Bymaster. As stated in the specification at pages 2-3, and page 12, lines 1-5, one of ordinary skill in the art would not be motivated to manufacture pharmaceutical compositions comprising citalopram by direct compression or filling into hard gelatin capsules, because it would be expected that such compositions would have an unacceptable variation in the content of citalopram. As stated in the specification, the small particle size of citalopram compared to fillers

would be expected to lead to segregation or de-mixing of the formulation. The inventors have surprisingly found that it is possible to manufacture pharmaceutical compositions comprising citalopram with an acceptable low variation in the content of citalopram, by using direct compression using citalopram crystals of a size comparable to the size of a filler. Even more surprisingly, the Examiners have found that it is possible to manufacture pharmaceutical compositions comprising citalopram with an acceptable low variation in the content of citalopram by direct compression using known, small-sized citalopram crystals (page 3, lines 17-23 and Examples 5 and 6).

In light of the foregoing, rejection of claims 1-35 is improper and rejection of claims 46-61 would be improper. Withdrawal of the rejections is respectfully requested.

## V. Conclusion

In view of the foregoing, it is believed that claims 1-35 are not indefinite, and that all claims 1-61 are neither anticipated by nor obvious over any of the cited references. Claims 1-61 are now believed to be in condition for allowance.

Favorable action is earnestly solicited.

Respectfully submitted,

Dated: September 18, 2001

John C. Todaro
Registration No. 36,036
Attorney for Applicant(s)

DARBY & DARBY
805 Third Avenue
New York, New York 10022
(212) 527-7700
Serial No. 09/730,380

5432/0I004

File No. 5432/0I004

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Ken Liljegren *et al.*

Serial No.: 09/730,380 Group Art Unit: 1625

Filed: December 5, 2000 Examiner: C. Aulakh

For: PHARMACEUTICAL COMPOSITION CONTAINING CITALOPRAM

---

## MARKUP TO AMENDMENT UNDER 37 C.F.R. §1.121

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. §1.121(c)(1)(ii), this Marked-Up Amendment shows all changes made to claims 1-35 in the attached Amendment.

1. (Amended) A solid unit dosage form comprising citalopram[, characterised in that it] which is prepared by direct compression of a mixture of citalopram base or a pharmaceutically acceptable salt and pharmaceutically acceptable excipients, or by filling of said mixture in a hard gelatine capsule.

2. (Amended) The solid unit dosage form according to claim 1[, characterised in that it] which is a tablet prepared by direct compression of a mixture of citalopram base or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients.

3. (Amended) The solid unit dosage form according to claim 1[, characterised in that it] which is prepared by filling a mixture of citalopram base or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients in a hard gelatine capsule.

4. (Twice Amended) The solid unit dosage form according to claim 1[, characterised in that it] which does not contain a binder.

5. (Twice Amended) The solid unit dosage form according to claim 1[, characterised in that it] which contains 2-60% w/w active ingredient calculated as citalopram base[, preferably 10-40% w/w active ingredient calculated as citalopram base and more preferred 15-25% w/w active ingredient calculated as citalopram base].

6. (Twice Amended) The solid unit dosage form according to claim 1[, characterised in that it] which contains a filler selected from lactose, sugars, [preferably sorbitol, mannitol, dextrose, and/or sucrose,] calcium phosphates, [preferably dibasic, tribasic, hydrous and/or anhydrous,] starch, modified starches, microcrystalline cellulose, calcium sulfate[, and/or] and calcium carbonate.

7. (Amended) The solid unit dosage form according to claim 6, [characterised in that] wherein the filler is a microcrystalline cellulose[, such as ProSolv SMCC90 or Avicel PH 200].

8. (Twice Amended) The solid unit dosage form according to claim 1[, characterised in that it] which contains a lubricant selected from metallic stearates [(magnesium, calcium, sodium)], stearic acid, wax, hydrogenated vegetable oil, talc and colloidal silica.

9. (Amended) The solid unit dosage form according to claim 8, [characterised in that] wherein the lubricant is magnesium stearate or calcium stearate.

10. (Twice Amended) The solid unit dosage form according to claim 1[, characterised in that it] which is substantially free of lactose.

11. (Twice Amended) The solid unit dosage form according to claim 1[, characterised in that] wherein the active ingredient is citalopram base.

12. (Twice Amended) The solid unit dosage form according to claim 1[, characterised in that] wherein the active ingredient is citalopram hydrobromide or citalopram hydrochloride.

13. (Amended) The solid unit dosage form according to claim 12, [characterised in that] wherein the active ingredient is citalopram hydrobromide.

14. (Twice Amended) The solid unit dosage form according to claim 12, [characterised in that] wherein the active ingredient is in the form of crystals with a median particle size below 20 μm.

15. (Twice Amended) The solid unit dosage form according to claim 12, [characterised in that] wherein the active ingredient is in the form of crystals with a median particle size of at least 40 μm[, preferably in the range of 40 - 200 μm, even more preferred 45 - 150 μm and most preferred 50 - 100 μm] .

16. (Amended) Crystals of a pharmaceutically acceptable salt of citalopram [suitable for use in a solid unit dosage form according to claim 15, characterised in that] wherein the median particle size of the crystals is at least 40 μm.

17. (Amended) Crystals according to claim 16, [characterised in that] wherein the crystals are of citalopram hydrobromide or citalopram hydrochloride.

18. (Amended) Crystals according to claim 17, [characterised in that] wherein the crystals are of citalopram hydrobromide.

19. (Twice Amended) Crystals according to claim 16, [characterised in that] wherein the median particle size of the crystals is in the range of 40 - 200 μm[, preferably 45 - 150 μm and even more preferred 50 - 120 μm].

20. (Amended) Method for manufacture of crystals of a pharmaceutically acceptable salt of citalopram having a median particle size of at least 40 μm [and suitable for use in a solid unit dosage form according to claim 15, characterised in that] wherein a solution of a pharmaceutically acceptable salt of citalopram in a suitable solvent system at a first temperature is first cooled down to a second temperature then seeded by addition of crystals of said citalopram salt followed by a holding time at said second temperature and a controlled cooling down to a third temperature whereupon said crystals are isolated by conventional solid/liquid separation techniques.

21. (Amended) The method according to claim 20, [characterised in that] wherein the median particle size of the crystals is in the range of 40 - 200 μm[, preferably 45 - 150 μm and even more preferred 50 - 120 μm].

22. (Twice Amended) The method according to claim 20, [characterised in that] wherein the dissolved substance is citalopram hydrobromide or citalopram hydrochloride.

23. (Amended) The method according to claim 22, [characterised in that] wherein the dissolved substance is citalopram hydrobromide.



b

24. (Twice Amended) The method according to claim 20, [characterised in that] wherein the solvent system comprises one or more alcohols and optionally water.

25. (Amended) The method according to claim 24, [characterised in that] wherein the solvent system is a mixture of methanol and water.

26. (Amended) The method according to claim 25[, characterised in that] wherein the methanol:water weight ratio is in the range of 5:1 to 50:1[; preferably 10: 1 to 30:1 and more preferred 15:1 to 25:1].

27. (Twice Amended) The method according to claim 20[, characterised in that] wherein the solvent:solute weight ratio is in the range of 0.5:1 to 5:1 [, preferably 0.7:1 to 2:1 and more preferred 0.9:1 to 1.5:1].

28. (Twice Amended) The method according to claim 20[, characterised in that] wherein said first temperature is in the range between 50°C and the refluxing temperature of the solvent system[, preferably between 60°C and the refluxing temperature and more preferred between 64°C and the refluxing temperature].

29. (Twice Amended) The method according to claim 20[, characterised in that] wherein said second temperature is in the range of 20-40°C[, preferably 25-35°C].

30. (Twice Amended) The method according to claim 20[, characterised in that] wherein said holding time is in the range of 30 minutes to 7 days[, preferably 1 hour to 4 days and more preferred 12 to 36 hours].

31. (Twice Amended) The method according to claim 20[, characterised in that] wherein said third temperature is in the range of 0-20°C[, preferably 5-15°].

32. (Twice Amended) The method according to claim 20[, characterised in that] wherein said controlled cooling down is a gradual cooling down over a time span in the range of 5 minutes to 6 hours[, preferably 15 minutes to 4 hours and more preferred 30 minutes to 2 hours].

33. (Twice Amended) The method according to claim 20[, characterised in that] wherein said isolation of the crystals of a pharmaceutically acceptable salt of citalopram from the mother liquor is performed by filtration.

34. (Amended) A solid unit dosage form prepared by directly compressing a mixture of citalopram [based] base or a pharmaceutically acceptable citalopram salt and pharmaceutically acceptable excipient.

35. (Amended) A solid unit dosage [from] form comprising citalopram prepared by filling in a hard gelatin capsule with a mixture comprising citalopram base and a pharmaceutically acceptable excipient.

Respectfully submitted,

Dated: September 18, 2001

John C. Todaro
Registration No. 36,036
Attorney for Applicant(s)

DARBY & DARBY
805 Third Avenue
New York, New York 10022
(212) 527-7700

::ODMA\WORLDOX\M:\5432\01004\TT0814.WPD